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Expiratory variability index is associated with asthma risk, wheeze and lung function in infants with recurrent respiratory symptoms

To the Editor:

Analysis of tidal breathing flow–volume (TBFV) curves is a convenient method to assess lung function in infants. We have shown that impedance pneumography (IP) is a valid method to assess overnight TBFV profiles in young children [1] and infants [2] and that certain specific curve shapes are related to symptom presentation and asthma risk [3]. We have also shown that the reduced variability of TBFV curves may be an indicator of airway obstruction in children [4–6]. However, in infants, it is unknown whether overnight TBFV variability is associated with respiratory symptoms or asthma risk.

TBFV variability has been expressed in several ways [4, 5, 7–10]. The recently introduced expiratory variability index (EVI) is derived by calculating correlations between expiratory TBFV curves, with low EVI indicating reduced variability of the curve shapes [6].

In this study, we hypothesised that TBFV variability, expressed as EVI, would be associated with wheeze and asthma risk in infants with recurrent respiratory symptoms.

The patient sample was previously described in detail [3]. Briefly, between January 2014 and May 2017 we recruited 43 infants referred to the Department of Allergy, Helsinki University Hospital, for infant lung function testing because of recurrent respiratory symptoms such as wheeze, cough and/or laborious breathing.

Children were classified by asthma risk by using loose criteria of the modified Asthma Predictive Index (mAPI). Children with a history of multiple episodes of wheeze (at least two) and who fulfilled one of the major criteria (parental history of asthma, atopic dermatitis, sensitisation to respiratory allergens), were considered to have a high risk of asthma. Children who did not have a history of wheeze or did not fulfil any of the major criteria above were considered to have low risk. Infants who fell between the criteria of high and low risk were considered to have an intermediate risk. Children with current respiratory infection were excluded.

Lung function was determined by measuring the maximal flow at functional residual capacity ($V'_{\max}\text{FRC}$) using rapid thoracic compression (Babybody Masterscreen, Jaeger Ltd., Germany) under sedation, and expressed as z-scores, adjusting for weight, length, and/or sex [11]. Fractional exhaled nitric oxide (F_{ENO}) was measured with the tidal online technique [12]. In a subgroup of infants ($n=14$), airway hyperresponsiveness (AHR) to methacholine was assessed as described earlier [13] and expressed as the provocative dose causing a reduction of 40% in $V'_{\max}\text{FRC}$ ($\text{PD}_{40}V'_{\max}\text{FRC}$). After lung function tests, an IP device (university-developed prototype [14]) was installed on the subjects for overnight recording at home. The study was approved by the institutional paediatric ethics committee of Helsinki University Central Hospital (approval no. 53/13/03/03/2012). All parents gave written informed consent.



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Impedance pneumography enables the measurement of the expiratory variability index (EVI) at home during a night's sleep in infants with recurrent respiratory symptoms. EVI is associated with asthma risk, symptoms and lung function. <https://bit.ly/2PF2cx8>

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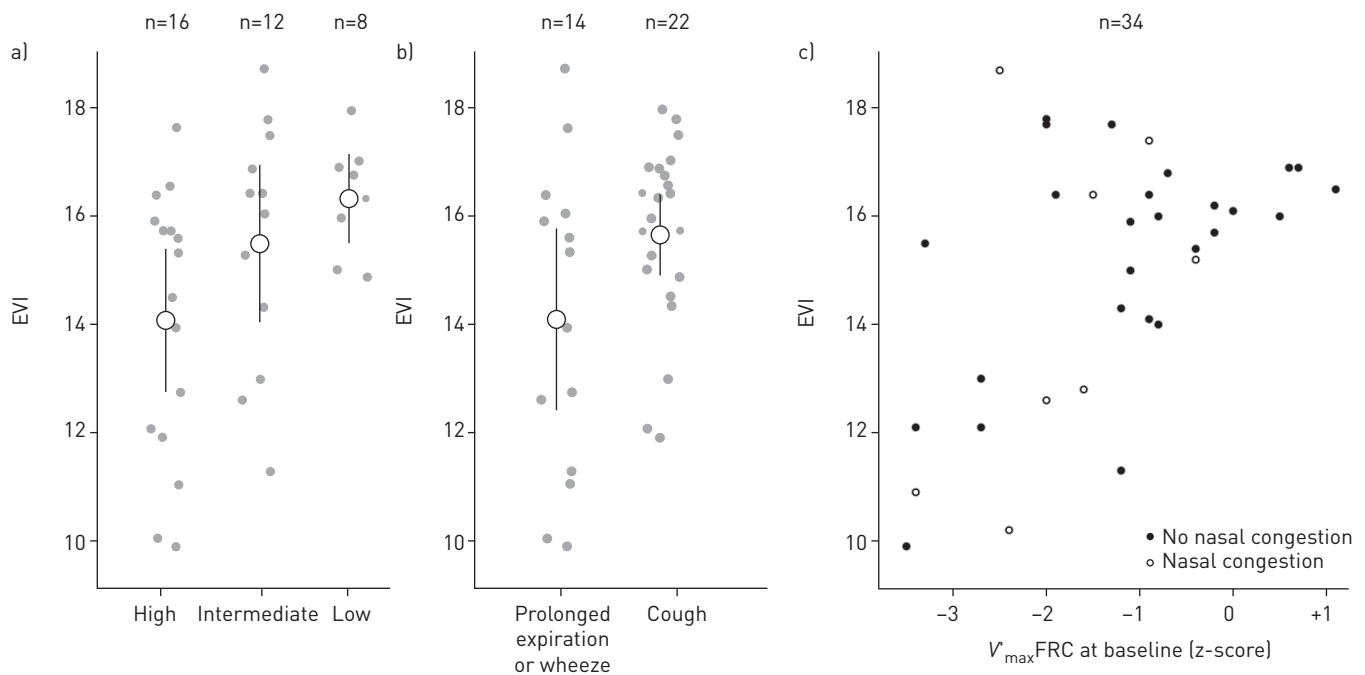


FIGURE 1 Expiratory variability index (EVI) compared with a) asthma risk groups ($p=0.022$), b) main symptom ($p=0.044$) and c) lung function ($r=0.52$, $p=0.02$). Circles and whiskers denote the mean and its 95% confidence interval, respectively. Dots represent results from individual patients. Two patients did not have maximal flow at functional residual capacity (V'_{\max} FRC) results available.

The previously recorded raw impedance signals were re-processed using commercial software (Ventica Analytics 2.1.0, Revenio Research Ltd., Finland) for the EVI.

EVI is derived by calculating Pearson correlations between all partial (15–45% of exhaled volume [5]), averaged (5-min window) TBFV curves recorded from the duration of the night's sleep resulting in a large number of correlation values. The output is given as $EVI = [\log_{10}[IQR(r)] + 2] \times 10$, where $IQR(r)$ is the interquartile range of the correlations. EVI thus measures the variability (dissimilarity) between TBFV curves compared to each other from all parts of the night, low EVI indicating low variability.

Parametric tests (t -test, ANOVA linear trend test) were used for comparing EVI between categories if EVI was normally distributed in each category (Shapiro–Wilks test p -value above 0.05). Otherwise a nonparametric test (Mann–Whitney U-test) was used (only for nasal congestion and atopic eczema). Association of EVI with continuous variables (V'_{\max} FRC, $PD_{40}V'_{\max}$ FRC and F_{ENO}) was assessed by Pearson correlation. No adjustments for multiple comparisons were made.

Overnight IP recordings at home were attempted on 43 infants, of which seven were rejected by the processing software because of bad electrode contact or malfunctioning of the prototype recorders. In 36 children IP measurements were successful allowing the calculation of EVI result. These children had a mean \pm SD (range) age of 12.8 \pm 5.1 (6.0–23.0) months, 20 (56%) of them had atopic eczema, nine (25%) positive skin prick test finding and they had had mean \pm SD 1.7 \pm 1.5 past wheeze episodes.

EVI was different between asthma risk categories (ANOVA linear trend test $p=0.022$, figure 1a), being lowest in the high asthma risk children. Children with prolonged expiration ($n=14$) or wheeze as the main symptom had lower EVI than those with only cough ($n=22$) (t -test $p=0.044$, figure 1b). EVI showed positive correlation with V'_{\max} FRC (Pearson correlation $r=0.52$, $p=0.002$, figure 1c).

EVI values from children with nasal congestion ($n=10$) were not statistically different from those without congestion (Mann–Whitney U-test $p=0.50$, figure 1c). This is in line with a recent finding in older children [6]. EVI was not correlated with age (Pearson correlation $r=-0.06$).

In overnight recordings, EVI was not significantly associated with AHR (Pearson correlation $r=0.11$, $p=0.70$), nor with atopic eczema (Mann–Whitney U-test $p=0.40$), skin prick test (t -test $p=0.49$) or F_{ENO} (Pearson correlation $r=0.21$, $p=0.24$).

In our previous study, we demonstrated that certain features of the shape of the expiratory flow–volume curve are associated with asthma risk and lung function in infants with respiratory symptoms [3]. In this study, we focused instead only on the variability of the curve shapes, expressed as EVI. Although the within-subject variation was large, we found EVI to associate with asthma risk, main symptom and lung function. The associations were only modest which may be attributed to small sample size and the low specificity and heterogeneity of the outcomes for asthma.

In this observational study, the results indicate reduced TBFV variability in infants with wheeze, which agrees with studies in adults with asthma [7] and COPD [8], children with asthma [4, 9], and infants with bronchopulmonary dysplasia [10]. This reduced variation in TBFV pattern, which has been attributed to reduced adaptability of the respiratory system during mechanical loading by airway obstruction [7], should be distinguished from the other phenomenon of increased variation in respiratory impedance or diurnal peak flow commonly known as characteristics of asthma [15].

EVI did not show association with AHR to methacholine. We speculate that decreased TBFV variability, as expressed by EVI, is more closely related to reduced lung function and adaptive mechanisms of tidal breathing than to AHR [3]. V'_{\max} FRC as a lung function measure has a wide inter-subject variability in infants, which explains the modest association with EVI. Moreover, the mechanisms of reduced V'_{\max} FRC vary between infants with respiratory symptoms. Depending on the mechanical resistive or elastic loading, neural and mechanical adaptive changes in breathing pattern may change and affect EVI differently [16]. It has been shown that sleep stages are a major contributor to normal TBFV curve changes which constitute normal (high) EVI [17].

Cough as the main symptom may have heterogeneous aetiology and it is an unsure sign of airway obstruction. This agrees with our finding of reduced EVI being more common in infants with wheeze as the main symptom. We acknowledge that due to the lack of a healthy control group and longitudinal data we are unable to estimate the proportion of abnormal EVI results in different patient groups or assess the specificity of EVI to estimate asthma risk in infants with recurrent respiratory symptoms. Furthermore, in this study, we did not estimate the interactions between sleep architecture and EVI, which need further studies.

In conclusion, the results suggest that variability of nocturnal tidal breathing, as quantified by the EVI parameter measured using the IP technique, is associated with asthma risk, symptoms and lung function in infants with recurrent respiratory symptoms. Provided that the findings are repeated in larger cohorts of infants, this technique may prove to be a useful, easy tool for objective assessment of respiratory symptoms in this age group where lung function testing is difficult.

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Conflict of interest: V-P. Seppä reports three patents with royalties paid to Revenio Group Inc. and is an employee of Revenio Group Inc., which commercialises impedance pneumography technology. J. Gracia Tabuenca has nothing to disclose. A. Kotaniemi-Syrjänen has nothing to disclose. K. Malmström has nothing to disclose. A. Hult is an employee of Revenio Group Inc., which commercialises impedance pneumography technology. A.S. Pelkonen has nothing to disclose. M.J. Mäkelä has nothing to disclose. J. Viik has three patents with royalties paid to Revenio Group Inc. L.P. Malmberg has nothing to disclose.

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